dehydrogenases. Many cases of so-called primary carnitine deficiency may be due to these or similar inborn errors of metabolism.

References

1. Engel AG, Angelini C. Carnitine deficiency of human skeletal muscle with associated lipid storage myopathy: a new syndrome. Science 1973; 179:899-902.
2. Di Mauro S, Trevisan C, Hays A. Disorders of lipid metabolism in muscle. Muscle Nerve 1980; 3:369-88.
3. Roe CR, Bohan TP. L-Carnitine therapy in propionic acidaemia. Lancet 1982; 1:1411-2.
4. Stanley CA, Hale DE, Whiteman DEH, et al. Systemic carnitine deficiency in isovaleric acidemia. Pediatr Res 1983; 17:296A. abstract.
5. Johnson MA. Skeletal muscle. In: Filipe MI, Lake BP, eds. Histochemistry in pathology. London: Churchill-Livingstone, 1983:89-113.
6. Johnson MA, Turnbull DM, Dick DJ, Sherratt HSA. A partial deficiency of cytochrome *c* oxidase in chronic progressive external ophthalmoplegia. J Neurol Sci 1983; 60:31-53.
7. Yates DW, Garland PB. Carnitine palmitoyltransferase activities (EC 2.3.1-) of rat liver mitochondria. Biochem J 1970; 119:547-52.
8. Turnbull DM, Sherratt HSA, Davies DM, Sykes AG. Tetracyano-2,2-bipyridineiron(III), an improved electron acceptor for the spectrophotometric assay of β-oxidation and of succinate dehydrogenase in intact mitochondria. Biochem J 1982; 206:511-6.
9. Davidson B, Schulz H. Separation, properties, and regulation of acylcoenzyme A dehydrogenases from bovine heart and liver. Arch Biochem Biophys 1982; 213:155-62.
10. Fong JC, Schulz H. Short-chain and long-chain enoyl-CoA hydratases from pig heart muscle. Methods Enzymol 1981; 71:390-8.
11. Schulz H, Staack H. 3-Ketoacyl-CoA-thiolase with broad chain length specificity from pig heart muscle. Methods Enzymol 1981; 71:398-403.
12. McGarry JD, Foster DW. An improved and simplified radioisotope assay for the determination of free and esterified carnitine. J Lipid Res 1976; 17:277-81.
13. Lloyd B, Burrin J, Smythe P, Alberti KGMM. Enzymatic fluorimetric continuous-flow assays for blood glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate. Clin Chem 1978; 24:1724-9.
14. Williamson DH, Mellanby J, Krebs HA. Enzymic determination of D(−)-hydroxybutyric acid and acetoacetate in blood. Biochem J 1962; 82: 90-6.
15. Keller U, Sonnenberg GE, Stauffacher W. Validation of a tracer technique to determine nonsteady-state ketone body turnover rates in man. Am J Physiol 1981; 240:E253-62.
16. Hegre CS, Halenz DR, Lane MD. The enzymatic carboxylation of butyryl coenzyme A. J Am Chem Soc 1959; 81:6526-7.
17. Tanaka K, Mantagos S, Genel M, Seashore MR, Billings BA, Baretz BH. New defect in fatty-acid metabolism with hypoglycaemia and organic aciduria. Lancet 1977; 2:986-7.
18. Mantagos S, Genel M, Tanaka K. Ethylmalonic-adipic aciduria: in vivo and in vitro studies indicating deficiency of activities of multiple acyl-CoA dehydrogenases. J Clin Invest 1979; 64:1580-9.
19. Gill A, Johnston DG, Ørskov H, Batstone GF, Alberti KGMM. Metabolic interactions of glucagon and cortisol in man — studies with somatostatin. Metabolism 1982; 31:305-11.
20. Sherratt HSA. Inhibition of gluconeogenesis by non-hormonal hypoglycaemic compounds. In: Hue L, Van der Werve G, eds. Short term regulation of liver metabolism. Amsterdam: Elsevier/North Holland, 1981:199-227.
21. Coates PM, Hale DE, Katz MR, Stanley CA, Hall CL. Detection of medium-chain acyl CoA dehydrogenase deficiency in leukocytes. Pediatr Res 1983; 17:288A. abstract.
22. Hale DE, Coates PM, Stanley CA, Cortner JA, Hall CL. Long-chain acyl-CoA dehydrogenase deficiency. Pediatr Res 1983; 17:290A. abstract.

PROGESTERONE SENSITIVITY AS A CAUSE OF RECURRENT ANAPHYLAXIS

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ANAPHYLACTIC or anaphylactoid attacks usually occur in immediate response to a specific inciting agent or event. Patients with recurring anaphylaxis in whom there is no evidence of an external cause are classified as having recurrent idiopathic anaphylaxis.[1,2] One such patient had weekly life-threatening anaphylactic episodes that were partly controlled with intensive medical therapy combined with tracheal fenestration; however, spontaneous remission of the attacks during lactation led to the suspicion of sensitivity to sex hormones. Three clinical observations confirmed this suspicion: provocative challenges with minute quantities of progesterone caused an anaphylactic event, inhibition of pituitary gonadotropin release by luteinizing hormone–releasing hormone analogue controlled the disease for nine months, and oophorectomy was curative.

Case Report

A 36-year-old woman had a lifelong history of seasonal allergic rhinitis and asthma, previous anaphylactic reactions to penicillin and streptomycin, and a strong family history of allergy. At age 33, after a two-year history of chronic "idiopathic" urticaria, she experienced acute anaphylactic attacks every 5 to 10 days and required frequent emergency treatment for hypotension, laryngeal edema, and asthma. Long-term management with hydroxyzine and cimetidine did not prevent the attacks but reduced their severity by preventing hypotension,[3] and long-term theophylline therapy ameliorated the bronchospasm. Because of the severity of the upper-airway angioedema, a permanent tracheal fenestration was created.[4] Medications that did not produce noticeable improvement included acetylsalicylic acid, indomethacin, vitamin E, prednisone (up to 100 mg per day for three months), and oral disodium cromoglycate.

The gynecologic history of this patient included intermittent use of oral contraceptives, seven pregnancies with four miscarriages, and parenteral progesterone administration during the completed pregnancies.

The results of physical examinations performed between attacks were unremarkable, but during attacks the patient had facial, lingual, laryngeal, and labial edema; diffuse wheezing and bronchorrhea; flushing and urticaria; tachycardia and substernal chest pressure; and abdominal bloating, with increases in girth up to 10 cm from base line. Electrocardiograms obtained during attacks revealed ST-segment depressions. Blood pressures recorded during attacks fell to 60/0 mm Hg until therapy with hydroxyzine and cimetidine was started; thereafter, hypotension was not a problem.

Skin tests for allergy to tree, grass, and ragweed pollens were positive; 24-hour excretion of urinary 5-hydroxyindoleacetic acid

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and vanilmandelic acid was normal; and C3, C4, and C1 esterase inhibitor activity was normal. Urinary histamine levels were elevated[5] on numerous occasions both during and between attacks, and plasma histamine levels were below 300 pg per milliliter.[6] A 14-day diet of rice, lamb, and water failed to influence the severity or frequency of the attacks. Skin biopsies and a bone-marrow examination did not show an increase in the number of mast cells, and bone scans were normal.[7]

Eight months after the onset of her attacks, the patient became pregnant. After a few, relatively minor episodes during the first trimester, the attack rate increased to one every three to seven days during the second and third trimesters, necessitating continuous use of diphenhydramine, cimetidine, and aminophylline. The patient gave birth to a normal boy who was breast-fed for seven months. No episodes of anaphylaxis occurred during the period of lactation. Two weeks after the spontaneous cessation of lactation, the attacks resumed, occurring approximately every five days.

Attempts were made to simulate hormonal conditions during lactation. Administration of oral contraceptives led to three attacks in a 36-hour period, necessitating urgent resuscitation. Metoclopramide (Reglan, A.H. Robins, Richmond, Va.) produced galactorrhea but had no effect on the illness. Intravenous challenge with luteinizing hormone–releasing hormone elicited three attacks in a 72-hour period.

Therapy with a long-acting analogue of luteinizing hormone–releasing hormone — D-Trp^6-Pro^9-Net-LHRH (LHRHa, 4 μg per kilogram of body weight, given daily and subcutaneously) — was initiated to suppress both gonadotropins and endogenous sex steroids. Physical and ultrasound examination of the pelvis and computed tomography of the cerebrum and sella turcica gave normal results. Pretreatment levels of luteinizing hormone, follicle-stimulating hormone, estradiol, progesterone, thyroxine, and basal and ACTH-stimulated cortisol were also normal. When LHRHa therapy was begun, the attack rate increased to one every three to four days (Fig. 1). One final menstrual period occurred, and thereafter, the patient had no evidence of ovulation, no menses, and no further anaphylactic episodes.

Urinary histamine levels were measured[8] both before and after the institution of therapy. The 24-hour urinary histamine excretion was 55.0±5.2 μg on 112 determinations and above 1000 μg on 3 determinations (normal mean ±S.E.M., 10.5±0.7 μg per 24 hours).[8] After LHRHa therapy was initiated, histamine excretion fell to 6±0.4 μg per 24 hours on six separate determinations over a six-month period.

Intradermal challenge with 10, 20, and 40 μg of medroxyprogesterone acetate (Depo-Provera, Upjohn, Kalamazoo, Mich.) given sequentially at 20-minute intervals resulted in diffuse pruritus and several urticarial lesions, followed in 90 minutes by diffuse urticaria, marked swelling of the tongue and abdomen, and bronchospasm. In two male and four female control subjects, medroxyprogesterone in doses up to 800 μg induced no reaction. The patient had no local or systemic symptoms after intradermal challenge with follicle-stimulating and luteinizing hormones (15 units of each), conjugated estrogens (Premarin, Ayerst Laboratories, New York), or diethylstilbestrol (200 μg).

Nine months after successful LHRHa therapy, the patient noted urinary incontinence and a pulling sensation in her lower abdomen. Second-degree uterine prolapse was noted, and hysterectomy with oophorectomy was performed. The patient has now been free of anaphylactic attacks for nine months, without any therapy.

Discussion

The diagnosis of recurrent anaphylaxis in our patient was based on the constellation of signs and symptoms, the demonstration of elevated urinary histamine levels, and the symptomatic improvement after treatment with H1 and H2 antihistamines. An extensive search for possible causes, including analysis of exposures to foods, chemicals, airborne allergens, drugs, physical activities, or emotional states, was initially unrewarding. In addition, diseases resembling anaphylaxis, such as carcinoid syndrome, pheochromocytoma, systemic mastocytosis, hereditary angioedema, aspirin sensitivity, and vasovagal attacks, were ruled out by a combination of the history, physical changes during attacks, and appropriate laboratory studies.

Our initial concerns were focused on managing the recurrent hypotension and syncope; administration of H1 and H2 antihistamines effectively controlled these problems. Laryngeal edema of life-threatening severity could be controlled only by tracheal fenestration,[4] a procedure that should be strongly recommended early in the clinical course of patients with similar problems. Glucocorticoids have been shown to be effective in other centers,[1] but they were not useful in this or other patients whom we have treated. Nonsteroidal antiinflammatory agents and disodium cromoglycate may reduce the clinical symptoms in some patients with systemic mastocytosis,[9,10,15] but they were not helpful in our patient. Acute bronchorrhea could be controlled only with inhaled atropine.[16] Thus, in this case, symptomatic therapy with antihistamines and bronchodilators proved to be the only effective treatment.

The patient's disease was so severe during the last six months of her pregnancy that long-term antihistamine and bronchodilator therapy was required, although there were concerns about possible influences on the fetus. Despite the prolonged exposure to cimetidine, a healthy child was born. The abrupt cessation of anaphylaxis post partum and the continuation of remission during lactation suggested that the alteration of hormonal status was having a beneficial influence. Thus, when lactation spontaneous-

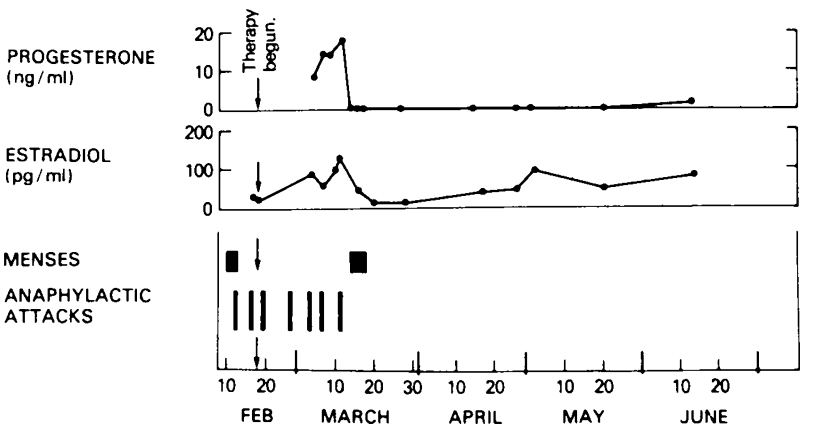

Figure 1. Response to LHRHa Therapy.

Plasma progesterone levels fell, menses ceased, and no subsequent anaphylactic episodes occurred except in response to intradermal challenge with medroxyprogesterone.

ly ceased and the anaphylactic attacks recurred, medical manipulation of the patient's hormonal status was attempted. Oral contraceptives, which suppress both pituitary hormone and endogenous ovarian hormone synthesis and release, exacerbated her disease, whereas induction of galactorrhea with metoclopramide had no effect.

When the patient was challenged with luteinizing hormone–releasing hormone, the frequency of anaphylactic attacks increased, suggesting that anaphylaxis was related to ovarian hormone secretion. LHRHa has been employed to suppress pituitary responsiveness to LHRH and is useful as a contraceptive and as a treatment for precocious puberty and prostate carcinoma.[11-14] In our patient, LHRHa therapy effectively reduced gonadotropin and progesterone levels, and the anaphylactic attacks ceased. Estrogen levels, although reduced, remained measurable. Consideration of oophorectomy was prompted by the development of uterine prolapse. Before recommending oophorectomy, however, we attempted provocative testing with follicle-stimulating hormone, luteinizing hormone, estrogen, and progesterone. Progesterone, but not the other drugs, provoked a mild immediate systemic reaction (in the absence of local skin reactions), followed by profound anaphylaxis 90 minutes later. After the oophorectomy, LHRHa treatment was discontinued and no subsequent anaphylactic attacks have occurred.

In summary, our patient's recurrent anaphylaxis responded to gonadotropin suppression with LHRHa and then to oophorectomy. Although we are not certain of the mechanism initiating the anaphylaxis, the patient's clinical course, response to gonadotropin suppression, and sensitivity to exogenous progesterone suggest that she was sensitive to native progesterone. It is possible that prior administration of parenteral or oral medications may have contributed to her sensitivity, and it is likely that this sensitivity contributed to her disease. The suggestion that endogenous progesterone was causally related to her attacks provides a fascinating new avenue of investigation in this and other related subjects.

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References

1. Bacal E, Patterson R, Zeiss CR. Evaluation of severe (anaphylactic) reactions. Clin Allergy 1978; 8:295-304.
2. Lieberman P, Taylor WW Jr. Recurrent idiopathic anaphylaxis. Arch Intern Med 1979; 139:1032-4.
3. Kaliner M, Sigler R, Summers R, Shelhamer JH. Effects of infused histamine: analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. J Allergy Clin Immunol 1981; 68:365-71.
4. Pruet CW, Kornblut AD, Brickman C, Kaliner MA, Frank MM. Management of the airway in patients with angioedema. Laryngoscope 1983; 93:749-55.
5. Warren K, Dyer J, Merlin S, Kaliner M. Measurement of urinary histamine: comparison of fluorometric and radioisotopic-enzymatic assay procedures. J Allergy Clin Immunol 1983; 71:206-11.
6. Dyer J, Warren K, Merlin S, Metcalfe DD, Kaliner M. Measurement of plasma histamine: description of an improved method and normal values. J Allergy Clin Immunol 1982; 70:82-7.
7. Rosenbaum RM, Frieri M, Metcalfe DD. Patterns of skeletal scintigraphy and their relationship to plasma and urinary histamine levels in systemic mastocytosis. J Nucl Med 1984; 25:859-64.
8. Myers G, Donlon M, Kaliner M. Measurement of urinary histamine: development of methodology and normal values. J Allergy Clin Immunol 1981; 67:305-11.
9. Roberts LJ II, Turk JW, Oates JA. Shock syndrome associated with mastocytosis: pharmacologic reversal of the acute episode and therapeutic prevention of recurrent attacks. Adv Shock Res 1982; 8:142-52.
10. Soter NA, Austen KF, Wasserman SI. Oral disodium cromoglycate in the treatment of systemic mastocytosis. N Engl J Med 1979; 301:465-9.
11. Comite F, Cutler GB Jr, Rivier J, Vale WW, Loriaux DL, Crowley WF Jr. Short-term treatment of idiopathic true precocious puberty with a long-acting analogue of luteinizing hormone-releasing hormone: a preliminary report. N Engl J Med 1981; 305:1546-50.
12. Berquist C, Nillius SJ, Wade L. Intranasal gonadotropin-releasing hormone agonist as a contraceptive agent. Lancet 1979; 2:215-7.
13. Comite F, Pescovitz O, Reith K, et al. Luteinizing hormone releasing hormone (LHRH) analog treatment of boys with hypothalamic hamartoma and true precocious puberty. J Clin Endocrinol Metab (in press).
14. Tolis G, Ackman D, Stellos A, et al. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. Proc Natl Acad Sci USA 1982; 79:1658-62.
15. Frieri M, Alling DA, Metcalfe DD. Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis: results of a double-blind clinical trial. Am J Med (in press).
16. Kaliner M, Marom Z, Patow C, Shelhamer J. Human respiratory mucus. J Allergy Clin Immunol 1984; 73:318-23.